Guidance for Industry

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2003
ICH

Guidance for Industry

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

Additional copies are available from:

Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm

Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2003
ICH

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Guidance for Industry[1]

Q1F Stability Data Package for Registration in Climatic Zones III and IV

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION (1) [2]

This guidance describes an approach to broader use of the ICH guidance *Q1A(R2) Stability Testing of New Drug Substances and Products* (hereafter referred to as the parent guidance) and outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in climatic zones III and IV (Grimm 1986, Schumacher 1974).

A. Background (1.2)

The parent guidance describes the stability data package for the ICH tripartite regions (the European Union (EU), Japan, and the United States), which are in climatic zones I and II. The parent guidance can be followed to generate stability data packages for registration applications in other countries or regions in zones I and II. For territories in climatic zones III and IV, the data package as described in the parent guidance can be considered applicable except for certain storage conditions. An approach for classification of countries according to climatic zones I, II, III, and IV can be found in the literature (Dietz 1993, Grimm 1998).

---

[1] This guidance was developed within the Expert Working Group (Quality) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, February 2003. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

[2] Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, February 2003.

The World Health Organization (WHO) has published a guideline "Stability testing of pharmaceutical products containing well established drug substances in conventional dosage forms" (WHO Technical Report Series, No. 863, Annex 5), updated in the "Report of the thirty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations," Geneva, 22-26 October 2001. The WHO guideline describes stability testing recommendations, including storage conditions for all four climatic zones.

The stability testing recommendations in this guidance are based on the parent guidance and the WHO guideline. To harmonize with the long-term storage condition for zones III and IV, the intermediate storage condition in the *general case* for zones I and II in the parent guidance is changed to 30°C ± 2°C/65% relative humidity (RH) ± 5% RH. This condition of 30°C ± 2°C/65% RH ± 5% RH can also be a suitable alternative to 25°C ± 2°C/60% RH ± 5% RH as the long-term storage condition for zones I and II.

B. Scope of the Guidance (1.3)

This document is an annex to the parent guidance and recommends the long-term storage condition for stability testing of a new drug substance or drug product for a registration application in territories in climatic zones III and IV.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. GUIDANCE (2)

A. Continuity With the Parent Guidance (2.1)

This guidance should be used in conjunction with the parent guidance and subsequently published annexes (Q1B, Q1C, Q1D, Q1E, Q5C).[3] The recommendations in the parent guidance and annexes should be followed unless specific alternatives are described within this guidance. The following sections of the parent guidance can be considered common to any territory in the world and are not reproduced here:

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage conditions for drug substance or product in a refrigerator
- Storage conditions for drug substance or product in a freezer
- Stability commitment

[3] These ICH guidances are available on the Internet at www.fda.gov/cder/guidance/index.htm.

- Evaluation
- Statements/labeling

B. Storage Conditions (2.2)

1. General Case (2.2.1)

For the *general case* (as described in the parent guideline), the recommended long-term and accelerated storage conditions for climatic zones III and IV are shown below:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/65% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 months

No intermediate storage condition for stability studies is recommended for climatic zones III and IV. Therefore, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in the ICH guidance *Q1E Evaluation of Stability Data* are applied.

2. Aqueous-Based Drug Products Packaged in Semipermeable Containers (2.2.2)

For aqueous-based drug products packaged in semipermeable containers (as described in the parent guidance), the recommended long-term and accelerated storage conditions for climatic zones III and IV are shown below:

Study	Storage condition	Minimum time period covered by data at submission
Long-term	30°C ± 2°C/35% RH ± 5% RH	12 months
Accelerated	40°C ± 2°C/not more than 25 % RH ± 5% RH	6 months

As described in the parent guidance, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio (see table below for examples). The ratio of water loss rates at a given temperature is calculated by the general formula (100 minus reference % RH) / (100 minus alternative % RH).

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

3. Tests at Elevated Temperature and/or Extremes of Humidity (2.2.3)

Special transportation and climatic conditions outside the storage conditions recommended in this guidance should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover extremely hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions (Grimm 1985).

Stability testing at a high humidity condition (e.g., 25°C/80% RH) is recommended for solid dosage forms in water-vapor permeable packaging (e.g., tablets in PVC/aluminum blisters) intended to be marketed in territories with extremely high humidity conditions in zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapor (e.g., aluminum/aluminum blisters), stability testing at a storage condition of extremely high humidity is not considered necessary.

C. Additional Considerations (2.3)

If it cannot be demonstrated that the drug substance or drug product will remain within its acceptance criteria when stored at 30°C ± 2°C/65 % RH ± 5 % RH for the duration of the proposed retest period or shelf life, the following options should be considered: (1) a reduced retest period or shelf life, (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

REFERENCES (3)

Dietz, R., K. Feilner, F. Gerst, and W. Grimm, "Drug Stability Testing — Classification of countries according to climatic zone," *Drugs Made in Germany,* 36:99-103, 1993.

Grimm, W., "Storage Conditions for Stability Testing — Long term testing and stress tests," *Drugs Made in Germany,* 28:196-202, 1985 (Part I) and 29:39-47, 1986 (Part II).

Grimm, W., "Extension of the International Conference on Harmonization Tripartite Guideline for Stability Testing of New Drug Substances and Products to Countries of Climatic Zones III and IV," *Drug Development and Industrial Pharmacy,* 24:313-325, 1998.

Schumacher, P., "Aktuelle Fragen zur Haltbarkeit von Arzneimitteln [Current questions on drug stability]," *Pharmazeutische Zeitung,* 119:321-324, 1974.